Remarks

Claims 1, 13, 38, 42, 48, 49 and 50 are pending. Claims 2-12, 14-37, 39-41 and 43-47 were previously cancelled. Claim 1 is amended to delete CHC_1-C_6 alkyl from the defined scope of G, and Claim 48 is amended to delete specific compounds within the scope of the CHC_1-C_6 alkyl definition.

Rejection Under 35 U.S.C. 112, First Paragraph

Claims 42 and 43 were rejected as failing to comply with the enablement requirement. Claim 43 is not pending and Applicants assume the Examiner intended Claim 50. Applicants traverse the rejection and request reconsideration. Applicants contend that the specification provides one skilled in the art with sufficient information to make and use the full scope of the presently claimed invention without "undue experimentation."

Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent application coupled with information known in the art without undue experimentation. MPEP 2164.01

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. MPEP 2164.01

Enclosed with this Reply is a Declaration from a named co-inventor of the claimed subject matter in the present application, Venkatesh Krishnan. In general, Dr. Krishnan's Declaration is directed toward in vitro and in vivo evaluations of exemplified and claimed compounds of the present invention as being ER beta selective agonists and for treating benign prostatic hyperplasia.

As evidenced by the scientific literature previously provided and discussed, as well as remarks below, one skilled in the art accepted the existence and mechanism of ER beta modulation as obviously correct at least by the provisional patent application filing date from which the present application claims priority. This acceptance included the antiproliferative effect of ER beta agonism on prostatic hyperplasia tissue. Further evidence exists in that others skilled in the art were searching for ER beta ligands for treatment of diseases as demonstrated by patents,

patent applications and a journal article provided and discussed below.

Dr. Krishnan's Declaration presents data and information on ER alpha and ER beta affinity and selectivity and functional activity and selectivity for exemplified compounds of the claimed invention. These data evidence the selectivity for and agonist activity of the presently claimed compounds for ER beta. This Declaration also presents data from a mouse BPH assay evidencing in vivo efficacy.

I. Enablement

All pending claims stand rejected under 35 U.S.C. 112, first paragraph, for allegedly not complying with the enablement requirement. Applicants respectfully traverse the rejection and request withdrawal of same. In support of the enablement rejection, the Examiner has based the rejection on the state of the art and therapeutic implications of modulating ER beta. Applicants respectfully contend the state of the art was far more developed than represented by the Examiner. Further, Applicants contend the therapeutic implications of agonizing ER beta for treating benign prostatic hyperplasia was clear to those skilled in the art prior to the United States provisional patent application filing date from which the present application claims priority.

A) The Enablement Requirement

Enablement refers to the requirement of 35 U.S.C. 112, first paragraph that the specification describe how to make and how to use the invention. The invention that one skilled in the art must be enabled to make and use is that defined by the claim(s) of the particular application. MPEP 2164

B) Test of Enablement

Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. Any part of the specification can support an enabling disclosure, even a background section that discusses the subject matter disclosed therein. Determining enablement is a question of law based on underlying factual findings. MPEP 2164.01

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. MPEP 2164.01

C) Undue Experimentation Factors

Factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure is enabling and whether any necessary experimentation is "undue" include, but are not limited to:

a) The breadth of the claims;

b) The nature of the invention;

c) The state of the prior art;

d) The level of one of ordinary skill;

e) The level of predictability in the art;

f) The amount of direction provided by the inventor;

g) The existence of working examples; and

h) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

It is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The Examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of non-enablement must be based on the evidence as a whole. *Wands*, 858 F2d at 737, 740, 8 USPQ2d at 1404, 1407. MPEP 2164.01(a)

D) How to Make the Claimed Invention

As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). MPEP 2164.01(b) (underlining added) Applicants' provided their position in the October 30, 2007 Communication and repeat those positions here.

E) How to Use the Claimed Invention

If a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. 112 is satisfied. MPEP 2164.01(c) (underlining added)

It is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation. If one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation, this would be sufficient to satisfy 35 U.S.C. 112, first paragraph. MPEP 2164.01(c)

When a compound or composition claim is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for non-enablement based on how to use. MPEP 2164.01(c) Applicants' provided their position in the October 30, 2007 Communication and repeat those positions here.

F) Working Example

Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed. MPEP 2164.02 (underlining added)

An in vitro or in vivo animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. MPEP 2164.02

If the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the Examiner has evidence that the model does not correlate. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995). MPEP 2164.02 Applicants' provided their position in the October 30, 2007 Communication and repeat those positions here.

G) Patent and Scientific Literature Evidencing Acceptance by Those Skilled in The Art

In addition to the established scientific principles and beliefs discussed in the Communication filed 30 October 2007, Applicants contend one of ordinary skill in the art accepted the assertions of ER beta agonist activity as useful for the treatment of BPH and/or prostate cancer as obviously correct. The following issued patents, published patent applications and journal article, all have a publication date prior to Applicants' earliest priority date for the present application. Applicants' assert these publications clearly evidence those skilled in the art accepted ER-beta modulation for use as a medicament for therapy as obviously correct. Either alone, or considered in combination with the scientific literature previously discussed, others skilled in the art have accepted ER-beta modulation for pharmacological therapy as an established scientific principle or belief.

Applicants respectfully direct the Examiner's attention to U.S. Patent 6,436,923 (assigned to Signal Pharmaceuticals, Inc.) filed March 17, 2000 and claiming priority from provisional application No. 60/240,909, filed March 17, 1999; and U.S. Patent 6,593,322 (also assigned to Signal Pharmaceuticals, Inc.) filed September 21, 2000, claiming priority from the patent application that matured into U.S. Patent 6,436,923 and provisional application No. 60/240,909 filed March 17, 1999.

Both of the referenced U.S. patents are directed toward selective ER beta modulating compounds, and pharmaceutical compositions containing those compounds. The compounds are stated to have selective ER beta modulator activity.

The Examiner's attention is also respectfully directed to U.S. Patent 6,518,301 (assigned to AstraZeneca) which was the national stage application under 35 U.S.C. 371 of PCT/GB00/01380, filed April 11, 2000 (published October 26, 2000 as WO 00/62765) claiming priority from provisional application No. 60/129,901, filed April 16, 1999. This patent is directed toward the use of compounds that are selective ER beta ligands as therapeutic agents in the treatment of various diseases.

Additional evidence of acceptance by those of ordinary skill in the art is an article by Meyers, et al., *J. Med. Chem.*, 44, 4230-4251 (2001), received by the Journal on June 6, 2001 and published October 16, 2001. This article is authored by a group of individuals from various Departments at the University of Illinois, Urbana, Illinois. The article discloses structure activity relationship (SAR) studies on ER beta selective ligands.

Finally, the Examiner's attention to U.S. Patent 6,794,403 (assigned to Wyeth) filed on December 4, 2002, claiming priority from provisional application No. 60/336,663, filed December 5, 2001. U.S. patent 6,794,403 discloses compounds as ER beta selective ligands useful for treating various described diseases.

Applicants respectfully contend these U.S. patents and the Meyer, et al. article clearly evidence that others skilled in the art accepted as obviously correct that selective ER beta modulators would be useful in the treatment of various diseases. Moreover, various other groups were actively pursuing a search for such selective ER beta ligands prior to Applicants.

II. Declaration

Enclosed with this Reply is a Declaration by Venkatesh Krishnan a named co-inventor of the claimed subject matter of the present application.

Dr. Krishnan's Declaration confirms he is one of the biologists who received compound samples from Eli Lilly and Company chemists, and tested or had tested those compounds in one or more of an Estrogen Receptor (ER) Binding Assay, Cell Based Transcriptional Assay and Mouse Prostate Assay. The assay protocols are included in Dr. Krishnan's Declaration and in the case of the ER Binding Assays is the assay protocol described in the present patent application at page 103, line 16 through page 104, line 18.

Generally, the ER Binding Assays are cell free competition binding assays that evaluates a test compound's property to preferentially bind to ER alpha or ER beta over the endogenous

ligand estradiol. As stated in the Declaration, those compounds of Examples 8-13, 15-18, 24-28 and 32 of the present patent application tested in the assay evidence (Exhibit 1) the tested compounds binding affinity to each of the human ER alpha and human ER beta receptors and the individual test compounds selectivity for binding to the human ER beta receptor compared to the human ER alpha receptor. Compounds that are selective for binding to the human ER beta receptor evidence a lower Ki value when compared to the Ki value obtained for the human ER alpha receptor.

The PC-3 ERE Reporter Assay is a cell based transcriptional assay designed to evaluate a test compound's binding property to ER alpha or ER beta and the induction of those receptors. As stated in Dr. Krishnan's Declaration, expression of a reporter gene (luciferace) by a test compound evidences agonist activity by that test compound while diminution of expression of that reporter gene by a test compound in the presence of or in comparison to a known agonist (diethylstilbestrol, DES, in this case) evidences antagonist activity by that test compound. In general, the data in Exhibit 2 for those compounds of Examples 8-13, 15-18, 24-28 and 32 tested in these assays, demonstrate agonist activity and functional selectivity in eliciting a response by ER beta over ER alpha.

Also included in Dr. Krishnan's Declaration is protocol and data from an in vivo CD-1 mouse ventral prostate assay. In this assay, test compounds are evaluated for their effects upon the weight of the ventral prostate in mice. The prostate, and in particular the ventral prostate, is an ER beta replete tissue. As stated in Dr. Krishnan's Declaration, compounds that reduce the weight of the prostate in small animal models, such as the mouse in vivo, demonstrate utility of that compound against benign prostatic hyperplasia. Also as stated in Dr. Krishnan's Declaration, the compounds of Example 10, Enantiomer A and Example 12-Enantiomer A, evidenced a statistically significant reduction in prostate weight in this assay.

Applicants respectfully contend data from the several assays in Dr. Krishnan's Declaration clearly evidence those compounds of the present invention tested in those assays are active, and selective ER beta agonists, and effective in treating benign prostate hyperplasia in these small animal models ("Patients" as defined in the specification includes mice, page 107, lines 19-22). Applicants further respectfully contend these small animal models are accepted by those skilled in the art as indicative of human clinical use of the compounds for treating benign prostatic hyperplasia.

Applicants' claimed compounds are ER beta agonists as stated in the specification of the present application.

While the complete functionality of ER beta (and ER alpha) in all tissues may not have been elucidated at the provisional filing date of the present application, the antiproliferative function of ER beta expression in prostate was known.

As more fully described in Applicants' Amendment and Response designated as filed on October 30, 2007, the present application is fully consistent and in compliance with *In re Jolles*, 206 USPQ 885 (CCPA 1980) and *Rasmussan v. SmithKline Beecham Corp.*, 75 USPQ.2d 1297 (Fed. Cir. 2005). The scientific literature as well as discovery and development activities by other pharmaceutical companies and scientists in academic institutions clearly evidences the skilled artisan accepted as correct the role of ER beta agonism in prostate tissue as antiproliferative. Others skilled in the art were pursuing the discovery of ER beta modulating agents for various therapeutic applications.

ER beta operates as an antiproliferative agent based on the experimental data. BPH is a proliferative disease. The discovery of novel ER beta agonists, the presently claimed invention, would be expected to beneficially treat BPH.

As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Rejection Under 35 U.S.C. 103(a)

Claims 1, 13, 38, 42, 48, 49 and 50 stand rejected under 35 U.S.C. 103(a) over Dodge, et al. (U.S. 6,630,508 B1; Dodge '508) in view of Dodge, et al. (U.S. 7,217,734 B2; Dodge '734).

Applicants respectfully traverse this rejection and request reconsideration. The Assignment documents of the present application for the provisional and the International application were provided as Exhibits 1 and 2 with the amendment dated October 30, 2007. Enclosed as Exhibit 6 is a copy of the Assignment document for the U.S. patent application that matured into U.S. Patent 6,630,508 B1. It should be seen that the Dodge '508 application is assigned to Eli Lilly and Company. At the time the present invention was made, the inventors were under an obligation to assign their invention to Eli Lilly and Company. Applicants respectfully contend the enclosed Assignment Exhibit 6 and previously submitted Exhibits 1 and 2 evidence Dodge '508 is not available as 35 U.S.C. 103(a) prior art against the presently claimed invention under 35 U.S.C. 103(c).

Applicants were all employees of Eli Lilly and Company at the time the present invention

was made. They were under an obligation to assign any inventions made to Eli Lilly and Company. Assignment Exhibit 1 is recorded at Reel 017859, Frame 0255 (6 pages). Assignment Exhibit 2 is recorded at Reel 020022, Frame 0687 (5 pages). The Assignment Exhibit 6 is recorded at Reel 012867, Frame 0768 (6 pages). Because the inventors of the present invention were, at the time the invention was made, under an obligation to assign and did assign such invention to Eli Lilly and Company, Applicants respectfully contend they have clearly demonstrated under 35 U.S.C. 103(c), Dodge '508 is not available as a 103(a) reference against the present application.

Applicants request reconsideration and withdrawal of the 35 U.S.C. 103(a) rejection.

Applicants respectfully contend the Examiner's factual positions for inquiries under Graham v. John Deere Co., 383 U.S. 1, 148 U.S.P.Q. 459 (1966) are erroneous. Necessarily, Applicants contend, positions taken by the Examiner based upon erroneous factual positions are also in error.

Applicants respectfully contend the Examiner on page 6 under Scope & Content of Prior Art MPEP 2141.01 has created a compound not exemplified in Dodge '508. Only through a careful and judicious selection from among the definitional variables in the disclosure (column 2, lines 29-52) can one arrive at the compound structure shown by the Examiner. The same error is applicable to the Examiner's position regarding the Dodge '734 reference.

The Examiner's position in the January 3, 2008 Office Action on page 6, under the sub-heading Differences between Prior Art and the Claims MPEP 2141.02 is in error because it is based upon comparing a compound from the Dodge '508 disclosure that is not exemplified against working examples of the presently claimed invention. The Examiner's position regarding the Dodge '734 disclosure and the working examples of the presently claimed invention is also in error for substantially the same reasons.

For at least the reasons stated above, Applicants contend the Examiner's conclusions regarding prima facie obviousness, rational and motivation, pages 7-8 of the January 3, 2008 Office Action, are in error as not being correctly factually based. Applicants contend in the absence of a correct factual basis, no prima facie case of obviousness has been established.

Double Patenting Issues

Claims 1, 13, 38, 42, 48 and 50 stand rejected under the non-statutory judicially created obviousness-type double patenting doctrine over Dodge '508 in view of Dodge '734. Applicants respectfully traverse this rejection and request reconsideration.

The elimination of CHC1-C6 alkyl from the definition of G in Claim 1 and specific compounds within the scope of that definition from Claim 48 removes this structural feature as a basis for an obviousness-type double patenting rejection over Dodge '734. Applicants request withdrawal of this rejection.

The Examiner's position regarding the positioning of the hydroxyl substituent on the 2-phenyl group of Dodge '508 is contrary to the preferences expressed in Dodge '508. At column 32, lines 17-40, Dodge '508 specifies that preferred selective ER beta compounds evidence a binding selectivity ratio (ER alpha Ki/ER beta Ki) of greater than 4. The compound of Example 5 has a binding selectivity ratio of 3.5. The binding ratio for the compound of Example 5 and the stated preference stand in direct contrast to the Examiner's position.

Applicants request withdrawal of an obviousness-type double patenting rejection based on Dodge '508.

Similarly, the Examiner's assertion regarding the positioning of the hydroxyl substituent at the 5 or 7 position (see Dodge '734, column 5, lines 35-50) of the dihydrobenzopyran portion of the molecules is also contrary to the preferences expressed in Dodge '734. At column 79, last line through column 80, line 28, preferred selective ER beta compounds are said to bind to the ER beta receptor with a binding selectivity ratio of greater than 4. As shown in Table 1, column 80, Examples 5 and 6 (5-hydroxy and 7-hydroxy, respectively; see column 56) evidence a binding selectivity ration of, respectively, 0.5 and 2.3. These binding ratios stand in direct contrast to the Examiner's position.

Applicants request withdrawal of an obviousness-type double patenting rejection based on Dodge '734.

Applicants respectfully contend the Examiner's evaluation of the Scope & Content of Prior Art MPEP 2141.01 (page 10 of January 3, 2008 Office Action) is factually in error as described above. Applicants also contend the Examiner has incorrectly used the disclosure of Dodge '508 rather than the claims of Dodge '508 and the claims of the present application, MPEP 804, chart II-B and 804 II-B-1.

When considering whether the invention defined in a claim of an application would have been an obvious variation of the invention defined in the claim of a patent, the disclosure of the patent may not be used as prior art. *General Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1279, 23 USPQ2d 1839, 1846 (Fed. Cir. 1992). (underlining added)

Similarly, whether considered alone for double patenting purposes, or in combination with Dodge '508, the Examiner has used the disclosure of Dodge '734 rather than the claims in the

factual analysis (Scope and Content, Differences) and conclusions (Prima Facie obviousness). As noted above, this is contrary to the referenced section of the MPEP.

Applicants respectfully contend the compounds of the present application are structurally distinct, as claimed, and no *prima facie* case of obviousness is present. Necessarily, Applicants contend the claims of *Dodge, et al.* '508 and/or '734 do not support a *prima facie* case of obviousness-type double patenting against the presently claimed compounds.

Dodge, et al. '508 and/or '734 does not teach, suggest or provide motivation to modify the apex carbon atom in the cyclopentane fused ring portion of the compounds.

Any teaching or suggestion in a reference of a preferred species or subgenus that is different in structure may weigh against the claimed modification and thus against a determination of obviousness. *In re Baird*, 16 F.3d at 382-83, 29 USPQ2d at 1552; *In re Jones*, 958 F.2d at 350, 21 USPQ2d at 1943 (reversing obviousness rejection of novel dicamba salt with acyclic structure over broad prior art genus encompassing claimed salt, where disclosed examples of genus were dissimilar in structure, lacking an ether linkage or being cyclic). For example, teachings of preferred species of a complex nature within the disclosed genus may motivate an artisan of ordinary skill to make similar complex species and thus teach away from making simple species within the genus.

Dodge, et al. '734 discloses optional substituents (Y^2 and Y^3) on the cyclopentyl, cyclohexyl or cycloheptyl fused ring portion of the molecule at the 11, 12 or 13 positions (see column 5, line 35 through column 6, line 14 of *Dodge, et al.*). At column 7, line 55 to bottom of column 7, *Dodge, et al.*, '734 teaches away from Y^2 and Y^3 substituents stating a preference for Y^2 and Y^3 are both H (Preferred embodiment (3)). Applicants contend this teaching away by *Dodge, et al.*, '734 would lead one skilled in the art away from modifying alternative positions of the cyclopentyl fused ring portion of the molecules as has been accomplished with the presently claimed compounds.

Although Applicants' do not acquiesce to the Examiner's position that a *prima facie* case of obviousness-type double patenting exists for the presently claimed invention over Dodge '508, Dodge '734, or a combination of the two Dodge references, included in Dr. Krishnan's Declaration as Exhibit 4 are data from Example 5 of Dodge '508 and Examples 10, 11, 5 and 6 of Dodge '734. These data address the alternative positioning of the hydroxyl substituents (Example 5 of Dodge '508 and Examples 5 and 6 of Dodge '734) and dimethyl and diethyl substituents (Examples 10 and 11 of Dodge '734). Each of Example 5 of Dodge '508 and Examples 10, 11, 5 and 6 of Dodge '734 are actual Examples within the specification, but more importantly, are

claimed in the respective references. As stated by Dr. Krishnan in his Declaration, the addition of those claimed substituents in the present patent application at the apex carbon atom of the cyclopentyl fused ring portion of the molecule afforded an unexpected improvement in Binding Selectivity (ER alpha Ki (nM)/ER beta Ki (nM)). The data upon which the Binding Ratio is calculated for the comparator compounds, as well as the claimed compounds of the present invention, has also been included in the Exhibits.

Applicants' respectfully contend that even if a *prima facie* case of obviousness-type double patenting is deemed to exist, despite the factual errors in analysis, the data in Dr. Krishnan's Declaration overcomes such *prima facie* case and establishes the independent patentability for the presently claimed invention. Applicants' request these obviousness-type double patenting rejections be withdrawn.

Conclusion

Applicants believe they have addressed each of the objections and rejections set forth by the Examiner in the Office Action, dated January 3, 2008. To the extent Applicants have inadvertently overlooked one or more of the objections or rejections set forth by the Examiner, Applicants respectfully request an opportunity to file a Supplemental Response in order to address such maters or to further respond in a subsequent communication.

In view of the evidence presented and remarks made herein, Applicants respectfully request favorable reconsideration of this application.

Respectfully submitted,

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